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2 CHTyper, a Web Tool for Subtyping of Extraintestinal Pathogenic *Escherichia coli* based on
3 the *fumC* and *fimH* Alleles

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23 Sir,

24 *Escherichia coli* can cause a variety of extra-intestinal infections, such as urinary tract

25 infection, meningitis, peritonitis and septicemia.

26 In 2012, Weissman *et al.* developed CH-typing, a two-locus, sequenced-based typing

27 scheme, for a fast determination of sequence types (STs) and sub-ST clonal groups of

28 extraintestinal pathogenic *E. coli* according to the multi-locus sequence typing (MLST)

29 scheme (1). CH-typing is based on *fumC*, one of the household genes used in the seven-loci

30 based MLST scheme (2), and an internal fragment of the type 1 fimbrial adhesin encoding

31 gene, *fimH*. In May 2017, we published a web tool for subtyping of *E. coli* based on the *fimH*

32 sequence (3). Here, we present a new web tool for CH-typing

33 (<https://cge.cbs.dtu.dk/services/chtyper/>) based on both *fumC* and *fimH*, which allows users to

34 obtain a CH-type from Sanger-generated sequences, fastq files, as well as assembled WGS

35 data.

36 In the paper by Weissman *et al.*, MLST and CH-typing were compared using 191 commensal

37 and pathogenic *E. coli* isolates and 853 clinical *E. coli* isolates (2). Here, CH-Types and

38 MLSTs were compared using assembled WGS data obtained from the Enterobase database

39 on July 3rd 2017 (<http://enterobase.warwick.ac.uk>). Only *E. coli* genomes meeting the criteria

40 of known MLSTs, according to the MLST scheme (1), and known *fimH* allele or *fimH*-null

41 (isolates without *fimH*) were included in the analysis, resulting in 35,704 *E. coli* genomes

42 from the Enterobase database. Discriminatory power was analyzed using the Simpsons index

43 of diversity (D) (4).

44 The individual MLST loci exhibited between 240 to 428 alleles based on the available *E. coli*

45 genomes obtained from EnteroBase, which resulted in 2,362 MLSTs, whereas the

46 combination of *fumC* and *fimH* resulted in 1,187 unique CH-types (Table 1). The

47 combination of *fumC* and *fimH* had a slightly higher discriminatory power (D = 0.9717 (CI;

0.9711-0.9723)) than the discriminatory power for MLST ($D = 0.9606$ (CI: 0.9596-0.9616). Similar observations were seen in the paper by Weissman *et al.* for the 191 commensal and pathogenic *E. coli* isolates (2). To determine the resolution of CH-typing for clinical field application, CHTyper was used to analyze genomic data from 243 third-generation cephalosporin-resistant *E. coli* isolates obtained from patients with bloodstream infection (5). Here, 48 different STs were obtained. ST131 was most common ($n=122$) and 18 STs had more than one isolate. Using CHTyper, 70 CH-Types were obtained for the 243 *E. coli* isolates (Table 2). The CH-typing further subdivided 12 of the 18 STs, with more than one isolate, e.g. ST131 was subdivided into five CH-Types (Table 2). Weissman *et al.* showed that specific CH-Types corresponded to specific STs and ST complexes with 95% accuracy, allowing good prediction of the MLST-based profile. Furthermore, CH-typing can detect the ST131 clonal subgroup *H30*, responsible for the current pandemic of fluoroquinolone and multi-drug resistant *E. coli* infections around the globe (6). Therefore, CH-typing can be used to study sub-ST clonal diversity or as a rapid screening test prior to selection for WGS. In summary, CHTyper provides a highly suitable tool that can act as a rapid alternative to conventional MLST surveillance and for outbreak detection.

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97 **TABLE 1.** Numbers of types found and D values of individual and combined loci of 35,704
 98 *E. coli* isolates from EnteroBase

Typing method	No. of types found	D (95% CI)
Single loci and MLST		
<i>adk</i>	311	0.8762 (0.8740-0.8783)
<i>fumC</i>	428	0.8882 (0.8863-0.8900)
<i>gyrB</i>	318	0.9205 (0.9193-0.9217)
<i>icd</i>	356	0.9107 (0.9095-0.9119)
<i>mdh</i>	275	0.9096 (0.9085-0.9106)
<i>purA</i>	266	0.8646 (0.8627-0.8665)
<i>recA</i>	240	0.8449 (0.8425-0.8474)
ST	2362	0.9606 (0.9596-0.9616)
<i>fimH</i> + <i>fimH0</i>	300	0.9495 (0.9488-0.9502)
Loci paired with <i>fimH</i>		
<i>adk</i> + <i>fimH</i>	985	0.9704 (0.9698-0.9709)
<i>fumC</i> + <i>fimH</i>	1187	0.9717 (0.9711-0.9723)
<i>gyrB</i> + <i>fimH</i>	1110	0.9720 (0.9714-0.9726)
<i>icd</i> + <i>fimH</i>	1082	0.9714 (0.9707-0.9720)
<i>mdh</i> + <i>fimH</i>	984	0.9711 (0.9705-0.9717)
<i>purA</i> + <i>fimH</i>	925	0.9705 (0.9699-0.9711)
<i>recA</i> + <i>fimH</i>	891	0.9702 (0.9696-0.9708)
ST + <i>fimH</i>	3167	0.9768 (0.9762-0.9774)

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102 **TABLE 2.** STs and CH-types for 243 third-generation cephalosporin-resistant *E. coli* isolates
103 obtained from patients with bloodstream infection

ST	CH-type(s) (n)
12	13-41 (1), 13-106 (4)
23	4-35 (1)
38	26-0 (2), 26-5 (14), 26-54 (1), 26-65 (1)
44	11-54 (2)
58	4-27 (1), 4-30 (2), 4-32 (1)
69	35-27 (10)
73	24-10 (1), 24-30 (1), 24-103 (1)
88	4-39 (1), 4-43 (1)
90	4-142 (1)
93	11-41 (1)
95	38-15 (1), 38-27 (1), 38-41 (2), 38-483 (1)
117	45-97 (1)
127	14-2 (2)
131	40-22 (1), 40-27 (14), 40-30 (95), 40-35 (1), 40-41 (11)
135	39-2 (1)
141	52-5 (1)
167	11-0 (3), 11-215 (1)
205	23-54 (1)
209	11-54 (1)
345	4-31 (1)
349	36-54 (1)
354	88-58 (1)
393	106-54 (1)
405	37- 27 (10), 37-29 (3)

410	4-24 (4)
421	38-0 (1)
443	19-24 (1)
450	11-34 (1), 11-54 (2)
453	6-31 (1)
550	14-54 (1)
603	4-517 (1)
617	11-0 (1), 11-29 (1)
624	4-27 (1)
636	108-0 (1)
648	4-0 (4), 4-27 (4)
977	188-25 (1)
1163	45-63 (1)
1177	26-65 (1)
1193	14-64 (2)
1248	29-31 (1)
1706	29-38 (1)
2509	95-60 (1)
2522	29-38 (1)
3014	41-34 (1)
3057	54-445 (1)
3285	6-35 (1)
3666	26-5 (3)
3995	4-27 (1)
5824	11-0 (1)

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